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CRITICAL REVIEW

Scientific production on the applicability of phenytoin in wound healing*

A PRODUÇÃO CIENTÍFICA ACERCA DA APLICABILIDADE DA FENITOÍNA NA CICATRIZAÇÃO DE FERIDAS

LA PRODUCCIÓN CIENTÍFICA ACERCA DE LA APLICABILIDAD DE LA FENITOÍNA EN LA CICATRIZACIÓN DE HERIDAS

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ABSTRACT

Phenytoin is an anticonvulsant that has been used in wound healing. The objectives of this study were to describe how the scientific production presents the use of phenytoin as a healing agent and to discuss its applicability in wounds. A literature review and hierarchy analysis of evidence-based practices was performed. Eighteen articles were analyzed that tested the intervention in wounds such as leprosy ulcers, leg ulcers, diabetic foot ulcers, pressure ulcers, trophic ulcers, war wounds, burns, preparation of recipient graft area, radiodermatitis and post-extraction of melanocytic nevi. Systemic use of phenytoin in the treatment of fistulas and the hypothesis of topical use in the treatment of vitiligo were found. In conclusion, topical use of phenytoin is scientifically evidenced. However robust research is needed that supports a protocol for the use of phenytoin as another option of a healing agent in clinical practice.

DESCRIPTORS

Phenytoin
Wound healing
Evidence-based nursing
Review

RESUMO

A fenitoína é um anticonvulsivante que vem sendo empregado na cicatrização de ferida. Os objetivos desta pesquisa foram: descrever como a produção científica apresenta o uso da fenitoína como agente cicatrizante e discutir sua aplicabilidade em feridas. Foi realizada, para tanto, revisão integrativa da literatura e análise pela hierarquia das práticas baseadas em evidências. Assim, analisaram-se 18 artigos que testaram a intervenção em feridas como úlceras de perna, por hanseníase, pé diabético, úlceras por pressão, tróficas, ferimentos de guerra, queimaduras, preparo da área receptora de enxerto, radiodermite e pós-extração de nevos melanocíticos. Uso sistêmico da fenitoína no tratamento de fístulas e a hipótese do uso tópico no tratamento do vitiligo foram achados. Conclui-se que a fenitoína tópica é uma evidência científica. No entanto necessita-se de pesquisas robustas que sustentem o uso protocolar da fenitoína como mais uma opção de agente cicatrizante na prática clínica.

DESCRIPTORES

Fenitoína
Cicatrização de feridas
Enfermagem baseada em evidências
Revisão.

RESUMEN

La fenitoína es un anticonvulsivo que se utiliza en la cicatrización de heridas. Los objetivos de esta investigación fueron: describir cómo la producción científica presenta el uso de la fenitoína como agente cicatrizante y discutir su aplicabilidad en las heridas. Se realizó una revisión integradora de la literatura y el análisis por la jerarquía de las prácticas basadas en las evidencias. Se analizaron 18 artículos que probaron la intervención en heridas como úlceras en la pierna por hanseniasis, pie diabético, úlceras por presión, tróficas, heridas de guerra, quemadura, preparación de la zona a injertar, radiodermitis y post extracción de nevos melanocíticos. Se encontró el uso sistémico de la fenitoína en el tratamiento de fístulas y la hipótesis del uso tópico en el tratamiento del vitiligo. Se concluye que la fenitoína tópica es una evidencia científica. Sin embargo, se necesita de investigaciones sólidas que sustenten el uso protocolar de la fenitoína como una opción más, considerándolo un agente cicatrizante en la práctica clínica.

DESCRIPTORES

Fenitoína
Cicatrización de heridas
Enfermería basada en la evidencia
Revisión.

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INTRODUCTION

Phenytoin is an anticonvulsant drug available in the market since 1937. It acts by blocking neuronal excitation by binding to sodium channels at rest, preventing them from becoming functional and generating excitatory action potentials⁽¹⁾. The possibility of its use as a healing agent began to be investigated by primary experimental studies in the field of dentistry, when, in 1939, hypergranulation of gingival tissue was recognized as its adverse effect, which suggested possible use of this drug as a healing agent in wounds⁽²⁻³⁾.

The exact mechanism through which phenytoin induces tissue healing is unclear, and the ways to apply it for this purpose are not standardized⁽⁴⁾. However, the dissemination of satisfactory results of empirical research about the performance of phenytoin in healing chronic wounds such as pressure, vascular and diabetic ulcers, has caught the attention of nurses that deal with this theme, such as stomatherapy expert nurses.

Phenytoin is a low-cost drug, and the study of its healing capacity for clinical practice is important. However, there is a need for research that can elucidate the subject and encourage its discussion in our context. Therefore, this research chose as the subject of investigative interest the scientific production on the therapeutic potential of phenytoin in the wound healing process in humans. The objectives were to describe how the scientific production presents the use of phenytoin as a healing agent and to discuss its applicability in wounds.

METHOD

An integrative literature review from 2003 to 2011 was performed. The temporal limit is justified by the publication of the study *The clinical effect of topical phenytoin on wound healing: a systematic review* by the British Journal of Dermatology⁽³⁾, which, although published in 2007, adopted temporal delimitation of 1963 to the middle of the year 2003.

Inclusion criteria were: a) articles that discussed the use of phenytoin in healing any kind of tissue injury in humans, b) available in Portuguese, English or Spanish.

The integrative review was divided into six stages: the first stage was the selection of the review question, which characterizes the definition of the subject to be studied; second stage was the selection of the bibliography. The third stage was the categorization of studies considering the data collection form validated by Ursi⁽⁵⁾.

The fourth stage was the review of inclusion criteria, critical reading, and systematic data analysis. The fifth step was interpretation of the results, discussion, organization and tabulation of information. And the sixth step was the presentation of the review to enable the critical

analysis of the findings by the reader, as recommended by the method adopted.

The guiding question of the review was: *How is the healing potential of phenytoin presented in the scientific literature regarding its clinical applicability in human wounds*. The selection of articles occurred in mid-April of 2012, in the following databases: Medical Literature Analysis and Retrieval System Online (MEDLINE), PubMed, Cochrane and Latin American and Caribbean Literature on Health Sciences (LILACS), accessed through the Virtual Health Library (VHL) portal. For the search of articles in the Latin American database, the descriptor *phenytoin* and the term *wounds* were used, and in the American databases, the descriptor *phenytoin* combined with the words *wound*; *wound healing* was used.

In MEDLINE, the descriptor *phenytoin*, when refined by combining it with the word *wound* using the boolean operator AND retrieved 92 studies. When the term *wound* was combined with *wound healing* using the Boolean operator AND, the research retrieved 82 studies. After duplicate exclusion, on a first analysis, considering titles and abstracts when available, 36 articles were selected. Repeating the same search model in PubMed and Cochrane, studies were duplicated, therefore no articles were included in this stage.

In the Latin American database, the descriptor *phenytoin* refined with the term *wounds* retrieved two studies, and one article was selected. The combination of the descriptor with the term *wound healing* retrieved no indication. Therefore, the preliminary selection was composed of 37 articles, which were categorized by the form adopted in this review. The categorization pointed to the need for full reading of the selected material, the texts being downloaded online and/or requested from institutional libraries. After a complete reading, 18 articles were included in the research, advancing to the fifth stage of this integrative review.

Data analysis used the level of evidence hierarchy, adopting standardized classification of evidence from one to seven: one corresponds to systematic review that examined randomized controlled trials, considered to be the type of research with highest reliability and scientific validity; Two: randomized clinical trial (RCT): with comparable groups and randomly divided in order to test interventions; Three: cohort study: study with observation and follow-up of the development of situations and/or injuries to the groups exposed to risks; Four: case-control study: interventions are applied to a given group, and the results are compared with a group which did not receive the intervention and serves as a parameter for comparison; Five: case series: the intervention is performed in several people and the outcomes analyzed and discussed in a particularized observational manner; Six: expert opinion: people considered *experts* opine on the possible interventions and the possible outcomes expected using

empirical work experience, without testing the mentally prepared hypotheses; Seven: Preclinical studies - studies conducted through experimentation on live animals or in controlled situations and laboratory test tubes.

From these criteria, force of evidence can be classified as strong, moderate and weak: research levels 1 and 2 have strong research evidence, levels 3 and 4 have moderate research evidence and levels 5 and 7 have weak research evidence. Beyond the force level, evidence has a degree of recommendation generated by the following rating: A - when the search result recommends the intervention, B - when the search result is not conclusive, and C - when the search result contraindicates the intervention⁽⁶⁾. This classification was adopted in this study.

RESULTS

The analysis of 18 articles in this literature review shows evidence of topical phenytoin as a healing agent applied to a range of chronic wounds and also acute wounds, in addition to its systemic use in the management of fistulas of the gastrointestinal tract. Beneficial

effects published urged the creation of the hypothesis of its topical use in the treatment of vitiligo, expanding the options for clinical investigation in other diseases that affect the skin, other than wounds themselves.

The Middle Eastern countries stand out in the scientific literature regarding the healing potential of phenytoin in humans, followed by: the United Kingdom, India, China and Brazil.

When considering the level of evidence and degree of recommendation, the United Kingdom is again highlighted, with two important strong-evidence studies published by the same author. Altogether the scientific production is typically published in English and performed in the academic medical area, especially the area of dermatological medicine, followed by endocrinology, surgery, neurology and dentistry. There was scientific production published in Portuguese, developed in the area of oncology nursing, as shown in Chart 1.

In the period of time delimitation studied in this integrative review, every year there was scientific production at an average two to three articles/year, and the year 2011 had four articles. This facet indicates an increased investigative interest on the theme in question.

Chart 1 - Studies that investigated the healing potential of phenytoin categorized by the hierarchy of scientific evidence - Rio de Janeiro 2012

Title/Reference (*)	Year/ Country	Design/ Research N	Interventions	Outcomes	Evidence /recomen- dation
The clinical effect of topical phenytoin on wound healing: a systematic review ⁽³⁾	2007 United Kingdom	Systematic review/ 14 RCT	Unspecified topical use in several types of wounds	Moderate evidences for the use in leg, leprosy, chronic, ulcers, diabetic foot. Limited evidences for the use in burns and war wounds	1/A
A systematic review of randomized controlled trials of treatments for inherited forms of epidermolysis bullosa ⁽⁷⁾	2008 United Kingdom	Systematic review /5 RCT	Oral pill 5mg/kg/day for Epidermolysis bullosa wound healing	No significant results compared to other interventions investigated	1/C
Nonhealing wounds – a therapeutic dilemma ⁽⁸⁾	2003 India	RCT/N 150 divided into 3 groups: human placenta extract, phenytoin and saline	100 mg pill macerated applied 1x/day in pressure, diabetic foot, leprosy and venous ulcers	Phenytoin group: healing in 48% cases, with full healing around the 21st day in group treatment and around the 45th day in group control	2/A
The use topical phenytoin for healing of chronic venous ulcerations ⁽⁹⁾	2011 Egypt	RCT/ N104 divided into study group (N54) and control (N50)	Manipulated lotion (1gr de phenytoin+ 25 mL lipossomal base) applied 1x/day for 8 weeks in venous ulcers	Full healing in N35 of the study group and in N26 of the control group. ↓ of ulcer surfaces was higher in the study groups. Burning sensation referred by N4 (7.4%)	2/A
Topical phenytoin versus eusol in the treatment of non- malignant chronic leg ulcers ⁽¹⁰⁾	2003 Tanzania	RCT/N 102 testing two interventions: Phenytoin (N50) x Eusol (N52)	Macerated pills applied to traumatic, inflammation, venous, diabetic, trophic ulcers, bites and burns	↓ pain, draining, and ↑ granulation tissue and healing more significant in the phenytoin group	2/A

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Title/Reference (*)	Year/ Country	Design/ Research N	Interventions	Outcomes	Evidence /recomen- dation
Topical phenytoin suspen- sion and normal saline in the treatment of leprosy tro- phic ulcers: a randomized, double-blind, comparative study ⁽¹¹⁾	2004 India	RCT/N45 comparing topi- cal phenytoin 2% and 4%	Gauze moistened with 100mg or 200mg pills dissolved in 5 mL solution of saline applied in leprosy ulcers 1x/day	Effectiveness in both cases, no significant difference	2/A
Topical phenytoin solution for treating pressure ulcers: a prospective, randomized, double-blinded clinical trial ⁽¹²⁾	2007 India	RCT/N 28 Intervention and control groups (saline) with assessment of the systemic phenytoin absor- tion rate	Gauze moistened with diluted intravenous solution 50mg/ml in saline (9 mL) topically ap- plied on pressure ulcers stage II 1x/day for 15 days	Healing evaluated by PUSH method evidencing slightly faster healing than the control group. Serum concentrations less than 0.2 ug/mL indicating negligible systemic absorption	2/A
A randomized clinical trial comparing hydrocol- loid, phenytoin and simple dressing for the treatment of pressure ulcers ⁽¹³⁾	2004 Iran	RCT/N83 paraplegic with 91 ulcers divided in 3 groups: hydrocol- loid, phenytoin and saline	Phenytoin cream applied 1x/day for 8 weeks	Hydrocolloid was more effective in healing with no significant differences between saline and phenytoin	2/B
A randomized clinical trial comparing hydrocol- loid, phenytoin and simple dressing for the treatment of pressure ulcers ⁽¹³⁾	2004 Iran	RCT/N83 paraplegic with 91 ulcers divided in 3 groups: hydrocol- loid, phenytoin and saline	Phenytoin cream applied 1x/day for 8 weeks	Hydrocolloid was more effective in healing with no significant differences between saline and phenytoin	2/B
Short report: treatment the effect of topical phenytoin on healing in diabetic foot ulcers: a randomized con- trolled trial ⁽¹⁴⁾	2011 United King- dom	RCT/N65 31N in the inter- vention group and N34 in the control group Measuring of the serum level of phenytoin up to 16 weeks	Phenytoin alginate applied 6mg/cm 1x/day	No significant difference among the groups Minimum systemic absorbance	2/C
Two percent topical phe- nytoin sodium solution in treating pyoderma gangrenosum: a cohort study ⁽¹⁵⁾	2010 Sri Lanka	Cohort study/N6	Gauze moistened in a solution of 2% phenytoin and placed on resistant pyoderma gangreno- sum wounds, 1x/day for 4 weeks	4 patients had fulls wound healing and 2 had partial resolution	3/A
Assessment of the effect of phenytoin on cutaneous healing from excision of melanocytic nevi on the face and on the back ⁽¹⁶⁾	2010 Brazil	Longitudinal case-control/N 100 patients with 200 lesions	Phenytoin cream 0.5% applied daily on injuries from removal of face and neck nevi	Lesions had more bleeding, exudate and hyperemia. ↑ edges, intense epithelialization and less healing time and good cosmetic effects on the scar	4/A
Wound bed preparation with 10 percent phenytoin oint- ment increases the take of swplit-hickness skin graft in large diabetic ulcers ⁽¹⁷⁾	2006 Jordã- nia	Case-control with hystological as- sessment /N16	Phenytoin 10% ointment based on vaseline applied 1x/day in wound bed preparation of diabetic foot ulcers for grafting, for up to 8 weeks	100% survival of the grafting in 12 patients, 80-90% in 3 and 60% in 1 patient	4/A
The impact of topical phe- nytoin on recalcitrant neuropathic diabetic foot ulceration ⁽¹⁸⁾	2009 Egypt	Prospective case series/N 32	Aerosol phenytoin 2% applied directly to diabetic foot wounds 1x/day in addition to usual treatment (instrumental debride- ment and cleansing with saline) for 8 weeks	50% patients had ↓ of wound size (mean 18.3% to 38.6% of the wound area)	5/A

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Title/Reference (*)	Year/ Country	Design/ Research N	Interventions	Outcomes	Evidence /recomen- dation
Phenytoin-induced lymphocytic chemotaxis, angiogenesis and accelerated healing of decubitus ulcer in a patient with stroke ⁽¹⁹⁾	2004 Greece	Comparative case study with biopsy analysis of 2 wounds in 1 patient	5mL IV phenytoin (250mg) applied on a pressure ulcer in sacral region in a paraplegic patient 1x/day for 2 weeks associated with standard treatment (debridement, antiseptic and dry gauze)	Faster healing by stimulating lymphocyte chemotaxis and super regulation of angiogenesis only in lesions treated with topical phenytoin	5/A
Therapeutic potential of phenytotin in radiodermatitis healing ⁽⁴⁾	2007 Brazil	Case report/N1	1mL phenytotin (50mg) diluted in 5ml saline applied 2x/day in radiodermatitis wound stage III with 5x3cm in cervical region for 13 days	Complete epithelialization which enabled cervical motion before impossible	5/A
Does phenytoin improve the healing of gastrointestinal fistulas? ⁽²⁰⁾	2011 Saudi Arabia	Case report/N2	300mg/day pills for 10 days via nasogastric tube in patients with pancreatic and colon-cutaneous fistula	Significant decrease of the effluent amount from the 4th day of use	5/B
Topical phenytoin treatment in bimaxillary osteomyelitis secondary to infantile osteopetrosis: report of a case ⁽²¹⁾	2006 Turkey	Case study/N1	Macerated pill applied in a thin layer of 20mg/cm ² and sterile gauze 1x/day for 2 weeks in bone exposition in oral cavity for osteomyelitis	Granulation and covering of bone exposure in 10 days	5/A
Phenytoin as a novel anti-vitiligo weapon ⁽²²⁾	2005 Iran	Expert opinion / hypothesis	Unspecified topic formula used in vitiligo lesions	Phenytoin would act by stimulating melanocytes. Animal experiments are suggested to test the hypothesis	6/A

The scientific production analyzed is characterized by the investigation of the healing potential of phenytoin by applying macerated pills directly on the wound, or the solution obtained from macerated pills or intravenous solution, both diluted in saline at a concentration of 5 or 10 mg/mL as shown in Table 1. Cream, ointment, alginate, lotion and aerosol were also other methods of application presented in the scientific production analyzed, although less frequently.

The clinical applicability of phenytoin for the purpose of healing wounds occurred primarily in diabetic foot and venous ulcers, followed by pressure and leprous ulcers. The other lesions were: osteomyelitis in the oral cavity, pyoderma gangrenosum, radiodermatitis grade III, and those resulting from excision of melanocytic nevi.

Overall, the studies were incomplete when describing how the phenytoin application was applied in the RCT, and the quality of methodological designs is still predominantly low, as was indicated in the pioneering work of Shaw and colleagues⁽³⁾.

DISCUSSION

Benefits from the use of phenytoin were associated with increased granulation tissue, angiogenesis, and decreasing of wound size. In cases when the drug was used systemically for the management of fistulas, there was a significant decrease of the effluent flow - which suggests a likely decline in the size of the fistulas that can be justified by the anatomic healing process, probably induced by phenytoin⁽²⁰⁾.

Although the mechanisms by which phenytoin heals human tissues are unclear, *in vitro* studies in laboratory animals and in human histopathology have contributed some information to the understanding of this phenomenon, by demonstrating stimulatory action of the drug on fibroblasts and collagen synthesis, cellular remodeling, inhibition of collagenase, and acceleration of autocrine and paracrine activity of growth factors through biochemical regulation of cell receptors involved^(3-4,8) and significant lymphocyte activation⁽²⁰⁾.

It is noteworthy that studies of moderate to strong evidence pointed to the analgesic effects of this drug for wounds⁽¹⁰⁾, and their authors mentioned the use of phenytoin as a *secure application*^(10,12,15), important factors when one is concerned about systemic absorption that application of topical phenytoin may trigger.

In terms of comparisons, it is emphasized that topical phenytoin showed healing potential higher than saline, although lower than hydrocolloid⁽¹³⁾. This fact makes the use of phenytoin as a healing agent attractive to health services devoid of greater resources for the acquisition of high-tech curative materials.

The scientific production on the healing potential of phenytoin is characterized by research on wounds that are classic problems for generating costs to the public system of global health, exacerbated in developing countries. Again it is important to consider that this drug was considered safe, inexpensive and effective in wound healing by several researchers considered in this integrative review^(4,8-12,16-17,19,21).

However, further research should be performed to fill in knowledge gaps on the topic. One example is that, notoriously, the same author who published a level-1 evidence study with inconclusive results regarding the application of the product on wounds, could not support the use of phenytoin as a healing product in diabetic foot ulcers when doing an experiment with evidence level 2 using alginate formulation, unprecedented in the scientific literature on the subject. However, the author did not discuss this preference⁽¹⁴⁾.

Surprisingly, phenytoin has been systemically used for the purpose of healing fistulas of the gastrointestinal tract, with encouraging results, although supported by weak research evidence and therefore with low strength of recommendation⁽²⁰⁾. However, it is a piece of information of interest to the field of oncology, including the use of phenytoin in healing radiodermatitis grade III⁽⁴⁾. Another study, not included in this review because it was not available at the time of the search in the indexed databases, investigated the use of phenytoin 0.5% for mouthwash in patients suffering from oral mucositis, resulting in improved quality of life of the group that received intervention⁽²³⁾.

The use of topical phenytoin in the form of 100 mg macerated pills diluted with 5 mL of 0.9% saline solution, applied 12/12 hr on a stage-4 pressure ulcer in the sacral region on a 50-year-old patient confined to bed for multiple sclerosis sequelae, was performed by Brazilian physicians and medical students in the northern region of the country. They reported that in 72 days the ulcer was completely filled with granulation tissue⁽²⁴⁾. This was a study approved by the Research Ethics Committee with evidence level 5, with degree of recommendation 5A. But this study was also not included in this review because it was not available in the indexed databases.

In the Middle East, spray phenytoin is available for wound healing, a product known as Healosol Spray: Wound Healing Promoter. Produced by the pharmacological company ACODIMA (Arab Company for Drug Industries Medical Appliances), it has as one of its indications the use in burn wounds⁽²⁵⁾, which again refers to the applicability of phenytoin in radiodermatitis burns, like studies number 4 and 11 of this review.

In Jordan in 2012, a preclinical study conducted on laboratory animals was published investigating the potential for wound healing of ethosuximide, barbituric acid and phenobarbital due to their structural similarity with phenytoin. The authors concluded that ethosuximide has clinical potential for the treatment of chronic wounds like phenytoin⁽²⁶⁾, making new hypotheses emerge from clinical research in the field of healing of tissue injuries. It can be inferred that researchers have begun to investigate the healing potential of drugs similar to phenytoin.

The formulation of phenytoin solution from pills, capsules or intravenous use is inconvenient for topical use because of low solubility and high pH (around 12), which may have stinging and burning sensations as adverse effects^(4,21). Hence the importance of the use of more specific formulations. In this sense, the Pharmacy School of the Royal College of Surgeons in Ireland - RCSI - has researched formulations that may provide greater solubility of phenytoin with a pH around 7-8 to be administered to wounds⁽²⁷⁾.

The global organization of pharmacovigilance – the US Food and Drug Administration - known by the acronym FDA, has approved the use of originally systemic products for the topical treatment of wounds, including anesthetics, antibiotics, and growth factors. In order to describe such situations in which a product is used for other purposes than those indicated in the package insert, the term *off-label prescription medication*⁽²⁸⁾ was created.

Misoprostol, lidocaine, nifedipine, gentamicin and metronidazole are examples of drugs being prescribed to treat wounds in cream formulations, macerated pills, gel and spray, using the concept that can be called, in Brazil, *off-label prescribing*⁽²⁸⁻²⁹⁾. It is a controversial practice, although it exists in our environment, such as the use of substances based on essential fatty acids (EFA) widely used as healing wounds, but still lacking quality studies to support use regarding safety and efficacy issues⁽³⁰⁾. The FDA accepts clinical studies that support the safety and efficacy of the applicability of the drugs in *off-label* uses, as well as the National Health Surveillance Agency - ANVISA – the regulatory agency in Brazil, which opens promising fields for research.

CONCLUSION

The integrative literature review performed in this study concluded that topical phenytoin has strong evidence

of beneficial effects on the healing process in venous, pressure, diabetic foot, leprosy, pyoderma gangrenosum ulcers and bed preparation for grafting. However, the studies conducted have moderate to low quality. More robust studies which support the use of phenytoin protocol as another option of healing agent in clinical practice are necessary.

Considering the way as scientific production presented the healing potential of phenytoin, the importance of incentives to produce studies that show its potential indications in the healing process are needed, which will greatly contribute to the revision and updating of care measures developed by nursing and other areas of healthcare, technology and innovation.

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